D-Dimer testing: the role of the clinical laboratory in the diagnosis of pulmonary embolism

B H Mavromatis, C M Kessler

Abstract
Pulmonary embolism is a common, yet often unsuspected and unrecognised disease associated with a high mortality. New, objective, “user friendly” and cost effective diagnostic strategies are being explored. D-Dimers, the fibrinolytic degradation products of crosslinked fibrin, have emerged as the most useful of the procoagulant activity and ongoing fibrinolysis markers. D-Dimer measurements are very sensitive in excluding a diagnosis of pulmonary embolism in the setting of normal values, a low clinical suspicion, and non-diagnostic lung scans. Several assays have been developed and are reviewed. (J Clin Pathol 2001;54:664–668)

Keywords: pulmonary embolism; D-dimer assay

The clinical condition now known as pulmonary embolism was described initially by RTH Laënnec in his 1819 exposé on “pulmonary apoplexy” (Greek ἀποτομήκτως). This sudden impairment of pulmonary function was part of a syndrome characterised by extensive parenchymal haemorrhage (“haemoptopic engorgement”) and symptomatic haemoptysis (“haemoptysical infarctus”). (“The lesion consists in an induration, which is partial, and never occupies a larger portion of the lung; . . . it is always well defined, of even character in its center and periphery. The surrounding parenchyma is entirely normal—the swollen part is very dark red.”)¹

Three decades later, the pathologist R Virchow established in an animal model that the pathophysiology of the disease was embolic, a concept rather unique for the time.¹ According to insurance statistics, pulmonary embolism is diagnosed at least 300 000 times/year (23/100 000 patients/year) in the USA, with an expected one year mortality rate of 19%.² Ten per cent of affected patients will experience recurrent events, with a subsequent death rate of 45%. The introduction of new and innovative therapeutic modalities for the treatment of pulmonary embolism, including the recent availability of low molecular weight heparin preparations and increasing use of thrombolytic treatments, have not altered the mortality and morbidity of this condition. In part, this can be attributed to the fact that most pulmonary emboli remain unsuspected and unrecognised before death;³ necropsy studies indicate that pulmonary emboli are overlooked as the primary or contributory cause of death in up to 84% of cases.³ Thus the crucial challenge of this disease resides in the development of new, rapid, specific, non-invasive, and “user friendly” objective diagnostic strategies, which can be used in a cost effective manner to amplify the accuracy of subjective clinical judgment and suspicion. The considerable morbidity and life threatening nature of thromboembolic diseases, such as pulmonary embolism, require prompt and accurate diagnosis so that appropriate treatment can be initiated. Diagnostic tests should ideally be highly specific and sensitive enough to provide accurate diagnoses so that expensive and invasive procedures can be avoided. Diagnostic test results should also help the clinician to assess the risk–benefit ratio of certain treatment modalities—for example, would the benefits of thrombolytic treatment for suspected massive pulmonary emboli, or for multiple small emboli with evidence of right ventricular dilatation, or for emboli associated with proximal deep vein thrombosis in the lower extremities outweigh the risks of treatment?

Clinical diagnosis
Clinical evaluation of the patient as an independent diagnostic modality for pulmonary embolism has been considered insufficiently accurate to yield rapid and definitive diagnoses in most cases. Among patients in a large general hospital who died from pulmonary embolism, the diagnosis (confirmed at necropsy) was unsuspected in 70% of patients.³ Ninety three per cent of these deaths occurred within 2.5 hours of the onset of symptoms, emphasising the importance of clinical suspicion and timely initiation of diagnostic testing and subsequent treatment. The prevalence of pulmonary emboli found in published postmortem studies has not changed over three decades, despite the availability of sensitive and specific non-invasive (ventilation perfusion lung scan, cine computed tomography (CT) scans, etc) and invasive (pulmonary arteriograms) screening techniques. The prospective investigation of pulmonary embolism diagnosis (PIOPED) study data suggest that clinical acumen can improve the accuracy of diagnosis and reduce the need for expensive confirmatory tests.⁴ That is, the combination of low clinical suspicion of pulmonary embolism and a low probability lung scan yields a very low post-scan incidence of pulmonary embolism (4%), thus obviating the need for pulmonary angiography. In contrast, approximately 90% of patients with high probability scans and high or intermediate clinical suspicion for pulmonary embolism do have emboli. Yet, the so called “classic” clinical and laboratory characteristics of pulmonary embolism are not evident in all patients.¹ Neither dyspnea nor tachypnea was observed in 12% of patients with the pulmonary infarction syndrome; a large number of patients with circulatory collapse attributable to pulmonary emboli were not dyspneic, tachypneic, or...
D-Dimer testing in the diagnosis of pulmonary embolism

Table 1  Methodologies available for measurement of D-dimer

<table>
<thead>
<tr>
<th>Assays</th>
<th>Commercial names</th>
<th>Methods</th>
<th>Characteristics</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latex particle assay</td>
<td></td>
<td></td>
<td>Lower sensitivity, lower NPV when compared with the ELISA method</td>
<td>Laaban et al (1997)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Easy to interpret, rapid, simple</td>
<td>Dale et al (1994)</td>
</tr>
<tr>
<td>Immunofiltration assay</td>
<td></td>
<td></td>
<td>Easier and faster than ELISA and latex assay</td>
<td>Turkstra et al (1998)</td>
</tr>
</tbody>
</table>

ELISA, enzyme linked immunosorbent assay; NPV, negative predictive value.

The spiral CT has emerged as a promising, convenient, and non-invasive diagnostic technique to visualise directly the pulmonary vessels in patients with suspected pulmonary emboli. However, subsegmental pulmonary emboli are more difficult to visualise in this setting, with both the test sensitivity and specificity decreasing from 94% to a sensitivity of 63% and a specificity of 89% in the detection of peripheral thrombi. In a small study,10 these subsegmental emboli seemed to be less clinically relevant, although larger studies need to be instituted to confirm these preliminary findings.

All these clinical data point to the need for a laboratory test geared to enhance our ability to make an accurate assessment when a pulmonary embolism is suspected.

The role of laboratory testing

The diagnosis of pulmonary embolism is difficult to exclude unless the ventilation perfusion lung scan and/or the spiral CT of the chest are normal. Because most pulmonary emboli are associated with intermediate probability ventilation perfusion lung scans, and because many patients with symptoms consistent with pulmonary embolism frequently have other
cardiopulmonary diseases, which could produce similar symptoms, there has been intense interest in including discriminatory laboratory testing in the diagnostic algorithm. Laboratory markers of procoagulant activity and ongoing fibrinolysis have been studied most extensively in the hope that, when combined with imaging tests, they can improve the predictive accuracy and efficiency of diagnosing pulmonary embolism; however, these markers are known to be raised in several medical disorders, which may or may not predispose to thromboembolic events—for example, carcinomas, hepatic and renal insufficiency, surgery, sepsis, stroke, and major trauma. Measurement of the D-dimer, the fibrinolytic degradation product of crosslinked fibrin, has emerged as the most useful dimer marker.

It is very sensitive, but non-specific for the diagnosis of deep vein thrombosis and pulmonary embolism; therefore, high values are not helpful in establishing the diagnosis of pulmonary embolism (PE); therefore, high values are not derived from patients with low pretest clinical probability for deep venous thrombosis or pulmonary embolus (table 4). SimpliRED D-dimer assay has gained recent popularity because its negative predictive value generally exceeds 95%; however, these data were derived from patients with low pretest clinical probability for deep venous thrombosis or pulmonary embolus (table 4).

D-dimer assays have lower sensitivities than ELISA assays. Prospective outpatient studies of the SimpliRED D-dimer assay have validated the negative predictive value of the assay to be as good as a normal ventilation perfusion lung scan, and better than a low probability lung scan. Successful therapeutic management has also been predicated on the results of the SimpliRED D-dimer assay. It may be safe to withhold anticoagulant treatment in those patients with a non-diagnostic lung scan, a normal SimpliRED D-dimer test, and a low probability D-dimer assay in detection of DVT or PE (table 4).

**Table 3** D-Dimer latex assays in detection of DVT or PE

<table>
<thead>
<tr>
<th>Number of patients (PE)</th>
<th>% Sensitivity</th>
<th>% Specificity</th>
<th>% PPV</th>
<th>% NPV</th>
<th>Cut off</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 (16)</td>
<td>81</td>
<td>60</td>
<td>76</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>64 (16)</td>
<td>94</td>
<td>58</td>
<td>43</td>
<td>97</td>
<td>500</td>
<td></td>
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<tr>
<td>183</td>
<td>68</td>
<td>77</td>
<td>25</td>
<td>95</td>
<td>350</td>
<td></td>
</tr>
<tr>
<td>117</td>
<td>88</td>
<td>71</td>
<td>84</td>
<td>75</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>85 (16)</td>
<td>94</td>
<td>94</td>
<td>96</td>
<td>96</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>386 (146)</td>
<td>100</td>
<td>47</td>
<td>53</td>
<td>96</td>
<td>2500</td>
<td></td>
</tr>
<tr>
<td>180</td>
<td>99</td>
<td>94</td>
<td>94.6</td>
<td>35</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>464</td>
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</tbody>
</table>

See footnotes to table 2.

**Table 4** SimpliRED D-dimer assay in detection of DVT or PE

<table>
<thead>
<tr>
<th>Number of patients (PE)</th>
<th>% Sensitivity</th>
<th>% Specificity</th>
<th>% PPV</th>
<th>% NPV</th>
<th>Cut off</th>
<th>Ref</th>
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<tr>
<td>86</td>
<td>94</td>
<td>66</td>
<td>38</td>
<td>98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>214</td>
<td>93 (proxDVT)</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>183</td>
<td>88</td>
<td>65</td>
<td>23</td>
<td>98</td>
<td>350</td>
<td></td>
</tr>
<tr>
<td>234</td>
<td>100</td>
<td>58</td>
<td>100</td>
<td>85–89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>73–80</td>
<td>77–80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1177 (197)</td>
<td>84.8</td>
<td>68.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>245</td>
<td>90 (PE)</td>
<td>83</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>265</td>
<td>93.3 (DVT)</td>
<td>45.2 (DVT)</td>
<td>34.3 (DVT)</td>
<td>95.6 (DVT)</td>
<td>94.2 (PE)</td>
<td></td>
</tr>
<tr>
<td>562</td>
<td>90.4 (PE)</td>
<td>62.2 (PE)</td>
<td>48.7 (PE)</td>
<td>98.1</td>
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<td></td>
</tr>
</tbody>
</table>

See footnotes to table 2.

DVT; deep vein thrombosis; NPV, negative predictive value; PE, pulmonary embolism; PPV, positive predictive value.
Table 5 Immunofiltration D-dimer assay in detection of DVT or PE

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>PPV %</th>
<th>NPV %</th>
<th>Cut off</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>92</td>
<td>100</td>
<td>42</td>
<td>57</td>
<td>100</td>
<td>500</td>
<td>Dale et al (1994)</td>
</tr>
<tr>
<td>183</td>
<td>95</td>
<td>33</td>
<td>14</td>
<td>98</td>
<td>500</td>
<td>Veitl et al (1996)</td>
</tr>
<tr>
<td>84</td>
<td>95.3</td>
<td>32</td>
<td>81.8</td>
<td>500</td>
<td></td>
<td>Kühle et al (1997)</td>
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<tr>
<td>180</td>
<td>90</td>
<td>63</td>
<td>60</td>
<td>91</td>
<td>250</td>
<td>Lindahl et al (1998)</td>
</tr>
</tbody>
</table>

See footnotes to table 2.

DVT, deep vein thrombosis; NPV, negative predictive value; PE, pulmonary embolism; PPV, positive predictive value.

Table 6 Immunoturbidimetric D-dimer assay in detection of DVT or PE

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>PPV %</th>
<th>NPV %</th>
<th>Cut off</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 (PE)</td>
<td>98 (DVT)</td>
<td>44 (DVT)</td>
<td>156</td>
<td>68</td>
<td>40</td>
<td>Knecht et al (1997)</td>
</tr>
</tbody>
</table>

See footnotes to table 2.

DVT, deep vein thrombosis; NPV, negative predictive value; PE, pulmonary embolism; PPV, positive predictive value.

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Editorial

201 Molecular pathology of solid tumours: translating research into clinical practice. Introduction and overview I Tomlinson

Reviews

203 Molecular pathology of solid tumours: some practical suggestions for translating research into clinical practice I P M Tomlinson, M Illyas

206 What we could do now: colorectal cancer R S Houlston

215 What we could do now: molecular pathology of bladder cancer M A Knowles

222 What we could do now: molecular pathology of gynaecological cancer C S Herrington

225 Commissioning laboratory services R D Turner

227 The IGF/IGFBP system in CNS malignancy W Zunkeller, M Westphal

Papers

230 Human glioma cells transformed by IGF-I triple helix technology show immune and apoptotic characteristics determining cell selection for gene therapy of glioblastoma A Ly, H T Duc, M Kalamarides, L A Trojan, Y Pan, A Sheeves, J-C François, T Noël, A Kane, D Henin, D D Anthony, J Trojan

240 Microsatellite instability and mutational analysis of transforming growth factor β receptor type II gene (TGFBR2) in sporadic ovarian cancer A J Alvi, J S Rader, M Broggini, F Latt, E R Maher

244 Identification of slide coagulase positive, tube coagulase negative Staphylococcus aureus by 16S ribosomal RNA gene sequencing P C Y Woo, A S P Leung, K W Leung, K Y Yuen


253 Application of laser capture microdissection and proteomics in colon cancer L C Latorre, S Curran, H L Mcloud, J E Fothergill, G I Murray

259 Absence of CCND1 gene amplification in breast tumours of BRCA1 mutation carriers S A J Vaziri, R R Tubbs, G Darlington, G Casey

264 Epstein-Barr virus infection in paediatric liver transplant recipients: detection of the virus in post-transplant tonsilslectomy specimens N Meru, S Davison, L Whitehead, A Jung, D Mutimer, N Rooney, D Kelly, G Niedobitek

270 Chromosomal abnormalities in liver cell dysplasia detected by comparative genomic hybridisation A Marchio, B Terris, M Mediche, P Piteau, A Dwenger, P Tiohlis, A Bernheim, A Dejan

275 Differential expression of the c3n (nov) proto-oncogene in human prostate cell lines and tissues M Maillard, B Cadot, R Y Ball, K Sethia, D R Edwards, B Perbal, R Tatoud
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B H Mavromatis and C M Kessler

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